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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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LAHIVE & COCKFIELD
28 STATE STREET
BOSTON MA 02109

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EXAMINER	
FORMAN, B	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No.	Applicant(s)	
	09/335,956	WARD ET AL.	
	Examiner	Art Unit	
	BJ Forman	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 December 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,10 and 12-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-7 9 10 12-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)

16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .

18)☐ Interview Summary (PTO-413) Paper No(s). _____ .

19)☐ Notice of Informal Patent Application (PTO-152)

20)☐ Other: .

DETAILED ACTION

1. This action is in response to papers filed 4 December 2000 in Paper No. 10 in which claims 1-7, 9, 10 & 12-18 were amended and claims 8 & 11 were canceled. All of the amendments have been thoroughly reviewed and entered. The previous rejections in the Office Action of Paper No. 8 dated 1 June 2000 under 35 U.S.C. 112, second paragraph are withdrawn in view of the amendments. The previous rejections under 35 U.S.C. 102(e) and 35 U.S.C. 103(a) are withdrawn in view of the amendments. All of the arguments have been thoroughly reviewed and are discussed below. New grounds for rejection are discussed.

Currently claims 1-7, 9, 10 & 12-18 are under prosecution.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

3. Claims 1-5, 7, 9, 13-15 & 17 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Gray et al. (U.S. Patent No. 5,447,841, filed 14 December 1990) in view of the teaching of Pinkel et al. (Proc. Natl. Acad. Sci. USA, 1988, 85: 9138-9142).

Regarding Claims 1 & 2, Gray et al. disclose a method of labeling individual mammalian chromosomes i.e. human chromosomes (Column 15, line 58-Column 16, line 57) in interphase

cells by *in situ* hybridization (Column 4, lines 57-62) the method comprising: providing chromosome-specific labeled probes (Column 16, lines20-23) and competitor DNA; combining the labeled probes and competitor DNA with human chromosomes in interphase cells under hybridization conditions wherein the labeled probes hybridize specifically to the human chromosomes, thereby labeling the chromosomes (Columns 11-12) wherein the methods are applied to interphase chromosomes by *in situ* hybridization (Column 4, lines 57-62).

Regarding Claim 3, Gray et al disclose a method of producing highly specific decoration of an individual target chromosome (Column 4, lines 63-67) comprising: providing chromosome-specific probes i.e. 21 (Column 16, lines20-23) and competitor DNA; combining the labeled probes and competitor DNA with human chromosomes in interphase cells under hybridization conditions wherein the labeled probes hybridize specifically to the human chromosomes, thereby producing highly specific decoration of individual human chromosomes (Columns 11-12) wherein the methods are applied to interphase chromosomes by *in situ* hybridization (Column 4, lines 57-62).

Regarding Claim 4, Gray et al. disclose the method wherein the labeled probes are probes comprising DNA inserts purified from a chromosome-derived recombinant library (Column 14, lines 29-49).

Regarding Claims 5, Gray et al. disclose the method wherein the labeled probes are selected from the group consisting of probes labeled with at least one fluorochrome, probes labeled with at least one member of a specific binding pair and probes labeled with an enzymes (Column 10, lines 16-46 and 67-68).

Regarding Claim 7, Gray et al disclose a method of assessing chromosome aberrations in human cells (Column 5, lines 20-34) by chromosomal *in situ* suppression hybridization comprising: providing labeled probes specific for chromosomal aberrations i.e. 21 (Column 16, lines20-23) and competitor DNA; combining the labeled probes and competitor DNA with human chromosomes under hybridization conditions wherein the labeled probes hybridize

specifically to the human chromosomes, and detecting the labeled probes in order to assess chromosomal aberrations (Column 5, lines 29-35) wherein the methods are applied to interphase chromosomes by in situ hybridization (Column 4, lines 57-62).

Regarding Claim 9, Gray et al. disclose the method for detecting chromosomes aberrations in human aneuploid cells (Column 5, lines 6-22 and Claim 9) comprising, treating the human aneuploid cells so as to render nucleic acid sequences available for hybridization (Column 15, line 66-Column 16, line 16) and combining the treated cells with a hybridization mixture comprising labeled human DNA derived from a specific chromosome (i.e. 21), competitor DNA (i.e. human genomic DNA) and non-human genomic DNA (i.e. lambda DNA) under conditions appropriate for hybridization (Column 16, lines 16-20 and 30-41) and detecting labeled human DNA derived from the specific chromosome hybridized to nucleic acid sequences from the cells (Column 16, lines 41-57) wherein the method is applicable to interphase cells (Column 4, lines 58-62).

Regarding Claim 13, Gray et al. disclose a method for detecting numerical alterations in a human chromosome in interphase cells (Column 4, lines 57-62 and Column 5, lines 6-22) comprising: selecting a human chromosome i.e. 21; treating cells to render nucleic acid sequences present in the cells available for hybridization (Column 15, line 66-Column 16, line 16); combining the treated cells with a hybridization mixture comprising labeled human DNA derived from a specific chromosome (i.e. 21), competitor DNA (i.e. human genomic DNA) and non-human genomic DNA (i.e. lambda DNA) under conditions appropriate for hybridization (Column 16, lines 16-20 and 30-41) and detecting labeled DNA from the selected chromosome to detect numerical alterations in a human chromosome (Column 16, lines 41-57) wherein the method is applicable to interphase cells (Column 4, lines 58-62).

Regarding Claim 14, Gray et al. disclose the method of Claim 13 wherein the selected human chromosome is number 21 (Column 16, lines 21-23 and Claim 10)

Regarding Claim 15, Gray et al. disclose the method of Claim 13 wherein the selected human chromosome is number 21 and the labeled human DNA derived from the selected chromosome is DNA inserts purified from a chromosome-derived recombinant DNA library (Column 14, lines 31-35).

Regarding Claim 17, Gray et al. disclose a method of identifying chromosome-specific DNA present in a selected mammalian chromosome (Column 5, lines 6-22 and Claim 1) comprising: selecting a mammalian chromosome i.e. 21; combining the selected chromosome with labeled DNA fragments derived from the selected mammalian chromosome (i.e. biotin-labeled human chromosome 21-specific DNA), competitor DNA (i.e. human genomic DNA) and carrier DNA (i.e. lambda DNA) (Column 16, lines 16-20) under conditions appropriate for hybridization of complementary nucleic acid sequences to occur (Column 16, lines 30-41) forming a complex of labeled DNA fragments with the selected mammalian chromosome in order to identify chromosome-specific DNA present in a mammalian chromosome (Column 16, lines 41-57) wherein the method is applicable to interphase cells (Column 4, lines 58-62).

Additionally, Pinkel et al., co-inventor of the above cited '841 patent, teach the method of labeling individual human chromosomes of interphase cells by *in situ* hybridization the method comprising the steps: providing chromosome-specific labeled probes (page 9138, right column, third full paragraph-page 9139, second paragraph) and competitor DNA; combining the labeled probes and competitor DNA with human chromosomes in interphase cells under hybridization conditions wherein the labeled probes hybridize specifically to the human chromosomes (page 9139, left column, "*In situ* Hybridization"), thereby labeling human chromosomes in interphase cells (page 9139, right column third full paragraph, lines 5-11 and Fig. 1e). Therefore, the teaching of Pinkel et al. confirms the co-authored teaching of Gray et al. wherein their method is applicable to interphase cells (Column 4, lines 58-62).

Response to Arguments

4. Applicant argues that Gray et al. fail to teach of suggest the claimed methods so as to enable one of ordinary skill in the art to practice the claimed methods without undue

experimentation because while Gray et al. teach their method is applicable to metaphase and interphase cells and they provide exemplification using metaphase cells, they do not provide specific guidance with regard to the myriad of factors required to perform *in situ* hybridization in interphase cells and they do not disclose a single exemplification using interphase cells but rather merely provide a starting point for further experimentation. This argument is not found persuasive because as stated above, Gray et al. teach their method is applicable to interphase cells (Column 4, lines 58-62) and the teaching of Pinkel et al. confirms that co-authored teaching of Gray et al.

Applicant further argues that Landegent et al. teach the method is not applicable to interphase cells because the sensitivity of the method is not sufficient for application to interphase cells. This argument is not found persuasive because the teaching of Landegent et al. is drawn to "detection of small (1-2kb) single-copy sequences" and not the claimed "chromosomes" and therefore, the teaching of Landegent et al. is not applicable to the method of Gray et al. which detects labeled chromosomes and the teaching of Pinkel et al. which confirms the method of Gray et al. as applicable to interphase cells.

5. Claims 1-5, 7, 9, 13-15 & 17 rejected under 35 U.S.C. 102(a) as being clearly anticipated by Pinkel et al. (Proc. Natl. Acad. Sci. USA, 1988, 85: 9138-9142).

Regarding Claims 1 & 2, Pinkel et al disclose a method of labeling individual human chromosomes in interphase cells (page 9138, right column, first full paragraph-page 9139, second paragraph) by *in situ* hybridization comprising: combining the labeled probes and competitor DNA with human chromosomes in interphase cells under conditions wherein the labeled probes hybridize specifically to the chromosomes (page 9139, left column, "*In situ* Hybridization"), thereby labeling human chromosomes in interphase cells (page 9139, right column third full paragraph, lines 5-11 and Fig. 1e).

Regarding Claim 3, Pinkel et al disclose the labeling produces highly specific decoration of an individual target chromosome i.e. 21 and 4 (page 9138, third full paragraph-page 9139, second paragraph).

Regarding Claim 4, Pinkel et al. disclose the DNA probes are specific DNA inserts purified from a chromosome-derived recombinant DNA library (page 9138, second full paragraph-page 9139, second paragraph).

Regarding Claim 5, Pinkel et al. disclose the labeled DNA probes are labeled with one member of a specific binding pair i.e. biotin (page 9138, right column, third full paragraph).

Regarding Claims 7, Pinkel et al disclose a method of assessing chromosome aberrations in human cells in interphase cells (page 9138, right column, first full paragraph-page 9139, second paragraph) by *in situ* hybridization comprising: combining the labeled probes and competitor DNA with human chromosomes in interphase cells under conditions wherein the labeled probes hybridize specifically to the chromosomes (page 9139, left column, "*In situ* Hybridization"), detecting the labeled probes in order to assess chromosomal aberrations human chromosomes in interphase cells (page 9139, right column third full paragraph, lines 5-11 and Fig. 1e).

Regarding Claim 9, Pinkel et al. disclose the method for detecting chromosomes aberrations in human aneuploid cells (page 9138, right column, first full paragraph-page 9139, second paragraph) comprising, treating the human aneuploid cells so as to render nucleic acid sequences available for hybridization and combining the treated cells with a hybridization mixture comprising labeled human DNA derived from a specific chromosome i.e. 21 & 4, competitor DNA i.e. human genomic DNA and non-human genomic DNA i.e. lambda DNA under conditions appropriate for hybridization (page 9139, left column) and detecting labeled human DNA derived from the specific chromosome hybridized to nucleic acid sequences from the cells (page 9139, right column third full paragraph and Fig. 1e).

Regarding Claim 13, Pinkel et al. disclose a method for detecting numerical alterations in a human chromosome in interphase cells (page 9138, right column, first full paragraph-page 9139, second paragraph) comprising: selecting a human chromosome i.e. 21 & 4; treating cells to render nucleic acid sequences present in the cells available for hybridization; combining the

treated cells with a hybridization mixture comprising labeled human DNA derived from a specific chromosome i.e. 21 & 4, competitor DNA i.e. human genomic DNA and non-human genomic DNA i.e. lambda DNA under conditions appropriate for hybridization and detecting labeled DNA from the selected chromosome to detect numerical alterations in a human chromosome (page 9139, right column third full paragraph and Fig. 1e).

Regarding Claim 14, Pinkel et al. disclose the method of Claim 13 wherein the selected human chromosome is number 21 (page 9139, left column first full paragraph).

Regarding Claim 15, Pinkel et al. disclose the method of Claim 13 wherein the selected human chromosome is number 21 and the labeled human DNA derived from the selected chromosome is DNA inserts purified from a chromosome-derived recombinant DNA library (page 9139, left column first full paragraph).

Regarding Claim 17, Pinkel et al. disclose a method of identifying chromosome-specific DNA present in a selected mammalian chromosome (page 9138, right column, first full paragraph-page 9139, second paragraph) comprising: selecting a mammalian chromosome i.e. 21; combining the selected chromosome with labeled DNA fragments derived from the selected mammalian chromosome i.e. biotin-labeled human chromosome 21-specific DNA, competitor DNA i.e. human genomic DNA and carrier DNA i.e. lambda DNA under conditions appropriate for hybridization of complementary nucleic acid sequences to occur forming a complex of labeled DNA fragments with the selected mammalian chromosome in order to identify chromosome-specific DNA present in a mammalian chromosome (page 9139, left column, right column third full paragraph and Fig. 1e).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-7, 9, 10 & 12-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gray et al. (U.S. Patent No. 5,446,841, filed 14 December 1990) and Smith et al. (Nature, 1986, 321: 674-679).

Regarding Claims 1- 6, Gray et al. teach the method of producing highly specific decoration of an individual target chromosome (Column 4, lines 63-67), comprising: providing chromosome-specific probes i.e. 21 (Column 16, lines20-23) and competitor DNA; combining the labeled probes and competitor DNA with human chromosomes in interphase cells under hybridization conditions wherein the labeled probes hybridize specifically to the human chromosomes, thereby producing highly specific decoration of individual human chromosomes (Columns 11-12) wherein the methods are applied to interphase chromosomes by *in situ* hybridization (Column 4, lines 57-62) wherein the probes are labeled using techniques known in the art and preferably fluorescently labeled (Column 10, lines 16-46 and 67-68) but they do not teach the specific fluorochrome. However, the claimed fluorochromes were well known and practiced in the art at the time the claimed invention was made as taught by Smith et al. who specifically teach commercially available Texas Red, rhodamine and fluorescein (page 675, Fig. 2). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply fluorochromes well know and practiced in the art to the fluorescent teaching of Gray et al. for the expected benefit of the convenience of commercially availability, the ability to perform real-time detection and for the economy of time and labor as taught by Smith et al. (page 674, right column).

Regarding Claims 10 & 12, Gray et al. disclose the method for detecting chromosomes aberrations in human aneuploid cells (Column 5, lines 6-22 and Claim 9) but they do not teach the method wherein the cells are human tumor cells (Claim 10) and wherein the tumor cells

are human glioma (Claim 12). However, Gray et al. teach the method for detecting chromosomal abnormalities is applicable to cancer diagnosis (Column 5, lines 33-35). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the Gray et al. method for detecting chromosomal abnormalities to tumor cells because tumor cells which were known to contain chromosomal abnormalities for the expected benefit of rapid and highly sensitive detection of tumor causing chromosomal abnormalities as taught by Gray et al. (Column 5, lines 29-35).

Regarding Claim 16, Gray et al. teach a method for determining over-representation or under-representation of a selected chromosome (Column 5, lines 6-22 and Claim 6) comprising, combining human cells treated so as to render nucleic acid sequences available for hybridization (Column 15, line 66-Column 16, line 16) and a hybridization mixture comprising labeled human DNA derived from a specific chromosome i.e. 21, competitor DNA i.e. human genomic DNA and non-human genomic DNA i.e. lambda DNA under conditions appropriate for hybridization (Column 16, lines 16-20 and 30-41) and detecting labeled human chromosome-specific DNA fragments hybridized to nucleic acid sequences from the cells (Column 16, lines 41-57 and Fig. 1). Gray et al. do not teach the cells are human tumor cells. However, Gray et al. teach the method for determining over-representation or under-representation of a selected chromosome is applicable to cancer diagnosis (Column 5, lines 33-35). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the Gray et al. method for detecting chromosomal abnormalities to tumor cells because tumor cells were known to contain chromosomal over and/or under-representation for the expected benefit of rapid and highly sensitive detection of tumor causing chromosomal abnormalities as taught by Gray et al. (Column 5, lines 29-35).

Regarding Claim 18, Gray et al. teach a method of identifying chromosome-specific DNA present in a selected mammalian chromosome (Column 5, lines 6-22 and Claim 1) comprising: selecting a mammalian chromosome i.e. 21; combining the selected chromosome with labeled

DNA fragments derived from the selected mammalian chromosome i.e. biotin-labeled human chromosome 21-specific DNA, competitor DNA i.e. human genomic DNA and carrier DNA i.e. lambda DNA (Column 16, lines 16-20) under conditions appropriate for hybridization of complementary nucleic acid sequences to occur (Column 16, lines 30-41) forming a complex of labeled DNA fragments with the selected mammalian chromosome in order to identify chromosome-specific DNA present in a mammalian chromosome (Column 16, lines 41-57) wherein the method is applicable to interphase cells (Column 4, lines 58-62) but they do not teach the complexes formed by hybridization with chromosome-specific DNA is isolated from the remaining substances. However, it was known and routinely practiced in the art to separate complexed DNA. It would have been obvious to one of ordinary skill in the art to modify the method of Gray et al. with routinely practiced procedures to obtain the claimed invention because one of skill in the art would have been motivated to separate the complexed DNA for the obvious benefit of analyzing the DNA of interest in isolation i.e. without extraneous cross-reacting or contaminating substances.

Response to Arguments

8. Applicant argues that Gray et al. fail to teach or suggest the claimed invention and specifically do not enable *in situ* suppression hybridization in interphase cells. This argument is not found persuasive for the reasons stated above. Specifically, Gray et al. teach the methods is applicable to interphase cells (Column 4, lines 58-62) and because Pinkel et al., co-inventor of the above cited '841 patent, teach the method of labeling individual human chromosomes by *in situ* hybridization of interphase cells wherein their method comprises the same method taught by Gray et al. (page 9138, right column, third full paragraph-page 9139, left column). Therefore, the teaching of Pinkel et al. confirms the teaching of Gray et al. wherein their method is applicable to interphase cells (Column 4, lines 58-62). Therefore, Gray et al. enable the skilled artisan to make and use the claimed invention.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:45 TO 4:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8742 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
February 14, 2001

PRIMARY EXAMINER